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Clinically cN0 breast cancer in elderly: What surgery?

Gennaro Limite, Rosa Di Micco, Viviana Sollazzo, Emanuela Esposito, Maria Cervotti*, Rita Compagna, Carlo De Werra, Bruno Amato, Pietro Forestieri

Department of Clinical Medicine and Surgery, Breast Unit, University of Naples Federico II, Italy

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ABSTRACT

Introduction: Breast carcinoma is the most common cancer in women worldwide. The incidence increases with age. Elderly patients have more advanced disease than younger ones, but they have a more favorable biologic tumor profile overall. The management of breast cancer in elderly is controversial. We report our experience with breast cancer in older than 65 years in the last 5 years, in order to assess how many axillary dissection may have been avoided, according to disease free survival (DFS) and overall survival (OS). **Materials and methods**: We enrolled in our retrospective study all over 65 year old patients referred to the Breast Unit of our Department of Clinical Medicine and Surgery at the University of Naples Federico II from January 2009 to December 2013. The end points were: evaluation of the rate of axillary treatment avoidable, DFS and OS. **Results**: We recruited 133 over 65 year old patients. Axillary lymph node was not palpable in 109 patients. The rate of involved axillae in patients without palpable nodes treated was 11.8%. The mean follow up was 35.7 months. At the time of data collection 3 patients had developed IBTR. No one had axillary recurrence, independently from the chosen treatment. 2 patients died for causes different from breast cancer. **Conclusion**: DFS and OS are the same both in patients with treated and no treated axilla. Even if evidences about the treatment of breast cancer in elderly are still controversial, each patient deserves a multidisciplinary approach to discuss the best treatment option.

1. Background

Breast carcinoma is the most common cancer in women worldwide. The incidence increases with age: approximately 50% of breast cancer occurs in women above the age of 65 and more than 30% above 70 years of age. As older women represent a fast growing part of the population, the treatment of breast cancer in elderly should be considered a new issue [1–6]. The management of breast cancer in elderly is controversial. The Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) updated the recommendations for elderly patient, but some aspects remains unclear. Treatment is largely based on extrapolation of study results from younger patients or physician's personal thought [7]. On a side breast cancer in elderly seems to have a better prognosis, on the other side the overall survival in older than 65 years decreases often due to comorbidities.

Older women are more likely estrogen receptor (ER) and progesterone receptor (PgR) positive breast cancer (85% in 80–84 years old vs. 60% in 30–34); whilst HER2 oncogene tends to be negative (10% vs 22%). Tumor size often increases because of delayed diagnosis. Major doubts are still about node involvement [8,9]. Even if elderly patients seem to have larger tumors and greater lymph node involvement, compared to younger ones, they have a more favorable biologic tumor profile overall. To further complicate the choice of the right treatment the age is correlated to comorbidities. Aging affects normal physiological process in terms of reductions in cardiac, respiratory and renal reserve, in addition to cognitive impairment. These factors may limit quality of life and adjuvant therapy rather than surgery. Comorbid diseases commonly associated to elderly could influence life expectancy and treatment tolerance. These variables influence treatment decisions in clinical practice, leaving space to discussion between physician and patient to achieve the best solution. Even if there is an emerging consensus that older women should be managed like younger patients, as regards surgical treatment, the functional

* Corresponding author. Department of Clinical Medicine and Surgery, Breast Unit, University of Naples Federico II, Via Pansini 5, 80131 Naples, Italy.
E-mail addresses: glimite@unina.it (G. Limite), rosadimicco@alice.it (R. Di Micco), vivianasollazzo@gmail.it (V. Sollazzo), emanuelaexpo@hotmail.it (E. Esposito), mariacervotti@alice.it (M. Cervotti), rita.compagna@libero.it (R. Compagna), dewerra@unina.it (C. De Werra), bramato@unina.it (B. Amato), p.forestieri@unina.it (P. Forestieri).

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status and the life expectancy modify this approach with the risk of undertreatment. The risk of dying from other causes often exceeds the risk of cancer recurrence, this is why the elderly patients are often treated less aggressively than younger patients [10].

We report our experience with breast cancer in women older than 65 years in the last 5 years, analyzing tumor characteristics, the treatment and the recurrence rate, above all in patients with clinically negative axillary lymph nodes. The choice of the treatment was based on an appropriate multidisciplinary assessment, including geriatric, oncologic and surgical evaluation, not neglecting patients' will. We studied the rate of axillary surgery in uninvolved axilla in order to assess how many axillary dissection may have been avoided, according to disease free survival and overall survival.

2. Materials and methods

We enrolled in our retrospective study all over 65 year old patients referred to the Breast Unit of our Department of Clinical Medicine and Surgery at the University of Naples Federico II from January 2009 to December 2013. Data on patient tumor clinical stage and characteristics, medical history, functional status, surgery, pathology, adjuvant therapies and follow up were collected from our Microsoft Access database. All patients underwent a multidisciplinary evaluation with a breast team composed by surgeon, radiologist, pathologist and oncologist to discuss the therapeutic plan, after a geriatric opinion on the basis of Comprehensive Geriatric Assessment (CGA).

The primary end point was to assess the rate of avoidable axillary treatment in over 65 year old patients according to pathology findings and recurrences, the secondary end points were disease-free survival (DFS) and overall survival (OS).

The surgical interventions proposed were: breast conservative surgery (BCS) or mastectomy, together with Sentinel Lymph Node Biopsy (SLNB), Axillary Lymph Node Dissection (ALND) or no axillary treatment.

BCS was proposed when tumor size was less than 3 cm and/or when feasible according to tumor/breast ratio. Mastectomy was indicated in tumors >5 cm or not amenable for BCS, retroareolar or multicentric disease. SLNB was performed in all patients with clinically negative axillary lymph node (cN0), with a good functional status and life expectancy >10 years according to geriatric assessment. ALND was performed in all patients with clinically positive axillary lymph nodes (cN+), in cN0 patients with contraindications to SLNB (allergy to methylene blue, noncompliance to lymphoschintigraphy or personal choice) with a good functional status and life expectancy >10 years according to geriatric assessment. No axillary treatment was proposed to all cN0 patients and was always performed according to personal patient choice, above all in cases of poor functional status and short life expectancy.

Patient preference was always taken into consideration.

Pathology investigations included local staging, when applicable; reporting histology, TNM parameters, ER, and PgR expression, ki-67 percentage, HER2 overexpression and grading.

Whole breast irradiation was performed in all patients <70 year old, undergone to BCS. Tamoxifen was administered to all hormone responsive patients younger than 80 years.

Mean age, median follow up, conservative interventions rates, total mastectomies, SLNB, ALND and no axillary treatment were retrospectively analyzed. Pathologic results were compared to clinical stage. Number and percentage of patients with axillary metastatic disease in cN0 were recorded for the total population and for three groups of different axillary treatment. Postoperative follow up examination were performed each week by the end of the first month after surgery, then three months after and six months after, providing clinical examination and annual mammography to assess loco-regional and axillary recurrences. At the time of data collection all patients were contacted by phone to verify health status.

The rate of involved and uninvolved nodes in cN0 patients were calculated, as well as the rate of node involvement in axilla treated patients, the rate of ipsilateral breast tumor recurrence (IBTR) and axillary recurrence, disease free survival (DFS) and overall survival (OS).

3. Results

A total of 133 over 65 year old patients referred to our Breast Service from January 2009 to December 2013. 3 of those were men. Mean age was 72.4 years (range: 65–92). 49 patients age spanned from 65 to 70 years, 63 patients from 70 to 80 years, 21 were older than 80. None of those presented with distant metastases at the time of surgery. BCS was performed in 101 cases, mastectomy in 32. In 24 patients axillary examination showed clinically palpable lymph nodes, thus ALND was performed. Axillary nodes were not palpable in 109 patients, 61 of those underwent SLNB, 16 ALND and 32 patients were spared from axillary surgery (Table 1). Final pathology report showed different histotypes: infiltrating ductal carcinoma (IDC) in 104 cases, infiltrating lobular carcinoma (ILC) in 18, others such as medullary, papillary or mucinous carcinoma in the remaining 11 cases. The mean diameter of the lesions was 20.5 mm. The T staging revealed: 82 cases of pT1, split as 3 pT1a, 16 pT1b and 63 pT1c; 45 were pT2, 3 pT3, and 3 pT4. Immunohistochemistry showed 120 ER positive, 114 PgR positive tumors. The average of the proliferation index ki-62 was <20% in 62 cases, ≥20% in 67 cases. The overexpression of proto-oncogene HER2 was present in 39 cases.

Patients with clinically involved nodes treated with ALND resulted in pN1 (14 cases), pN2 (7 cases), pN3 (3 cases). Among treated cN0 patients (77) we reported 9 cases of axillary metastases, of these resulting in 3 micrometastases and 6 partial or diffuse metastases of one single node, in most cases (3 involved nodes in one case) (Table 4). The rate of axillary involvement with clinical non palpable node disease treated with SLNB or ALND was 11.8% (9/77). In these patients axillary dissection was not completed for both surgeon and patient choice.

The rate of uninvolved axillary at final pathology (pN0) in the same cohort of cN0 patients with treated axilla was 88.3% (68/77). Considering all patients (cN0 and cN+), whose axilla was treated (101 cases), the rate of node involvement was 32.7% (33/101) (Table 2).

Only 37 patients underwent whole breast irradiation after surgery. 100 patients received adjuvant hormone therapy. None of the patients has been lost at follow up.

Median follow up was 35.7 months (range: 6–66 months). At the time of data collection 3 patients developed IBTR and underwent salvage mastectomy. No one had axillary recurrence, independently from the opted treatment. 2 patients died from causes other than breast cancer (Table 3).

Table 1
Clinical features and surgical treatment.

	SLND	ALND	NO surgery	Total
Age				
65–69	28	12	9	49 (36.8%)
70–74	19	16	8	43 (32.3%)
75–79	9	6	5	20 (15.0%)
≥80	5	6	10	21 (15.8%)
Clinically non palpable axillary nodes	61	16	32	109 (90.0%)
Breast conserving surgery	52	22	27	101 (75.9%)
Total mastectomy	9	18	5	32 (24.0%)
Total	61	40	32	133

At the time of the study the DFS was 97.7% (3/130) due to IBTR-. Axillary recurrence rate was 0%, whereas the OS was 97.7% (130/133).

4. Discussion

The treatment of breast cancer in older women still represents a challenge for the surgeon. Several factors, different from younger patients, influence the prognosis of the breast disease and the treatment tolerance in elderly, thus guiding therapy. Breast cancer in elderly deserves the same attention than in youth. Age and comorbidities must be taken into account, but how and when they should affect the current practice is a complex issue. Older patients with a short life expectancy, if not suitable for surgery, may adequately be treated with endocrine treatment alone [11]. Patients with hormone-negative receptors and operable breast cancer need a careful surgical evaluation. Comorbidities often affect adjuvant treatment, such as cytotoxic chemotherapy option, whose benefit in elderly has limited evidence [12]. Surgery related morbidity for breast cancer is minimal and patient's diseases are rarely significant in determining whether she should be eligible for it. The role of surgery is crucial in local control and accurate staging. The adequate local control of disease is important and may have a significant effect on survival in women with a life expectancy of between 10 and 15 years [13]. However, surgical treatment may still be appropriate in such patients to avoid the development of distressing symptoms, such as pain, ulceration and bleeding for cancer local progression. The accurate staging is related to tumor volume and axillary lymph node involvement. So if the benefits of the surgical intervention are undoubted, the treatment of the axilla is still object of debate as in younger as in older patients. Certainly axillary clearance in cases of palpable or suspicious nodes, at ultrasound scan or needle aspiration citology, is mandatory.

Management and prognosis of patients presenting with clinically negative axillary lymph nodes have been the main focus of our study. The role of careful preoperative staging is crucial in order to choose adjuvant therapies for patients above. Whilst the benefit of chemotherapy in elderly lacks as well as of the chest wall RT after mastectomy, and remain limited to very few cases, the role of axillary staging in clinically (and/or US, citology) uninvolved axilla may be discussed. Fisher et al. were the first to evidence that lymph node involvement was an indicator, not a governor of distant spread and that prognosis was mainly determined by tumor biology [14]. Martelli et al. with 15 years' follow up demonstrated that elderly women with T1N0 ER-positive breast cancer treated with BCS and randomized for ALND versus no axillary dissection had no differences in OS or breast cancer mortality [15]. The International Breast Cancer Study Group (IBCSG) trial randomized elderly patients with cN0 ER-positive operable breast cancer for axillary dissection versus observation, demonstrating no difference in OS or DFS after 6.6 years of follow-up [16].

In order to choose what patients benefit from primary surgery and how to treat them, we included Comprehensive Geriatric Assessment (CGA) in our preoperative multidisciplinary assessment. The CGA is a multidimensional, interdisciplinary diagnostic process to determine the medical, psychological and functional capabilities of elderly patients in order to develop a coordinated plan for their treatment [17]. Recently it has been used to assess the

Table 2
Clinical and Pathologic findings in our population.

	SLND		ALND		NO surgery	Total
	pN0	pN+	pN0	pN+	pNx	
Surgery						
Breast conserving surgery	46	6	9	12	27	101 (75.9%)
Total mastectomy	6	3	6	12	5	32 (24.0%)
Histological type						
Ductal carcinoma	43	9	9	19	24	104 (78.2%)
Lobular carcinoma	5	0	6	3	4	18 (13.5)
Other infiltrating carcinoma (mucinous, papillary, medullary)	4	0	1	2	4	11 (8.3%)
Multifocal/multicentric disease	3	2	2	5	2	13 (9.8%)
Stage						
pT1	39	6	7	6	24	82 (61.7%)
T1a	1	–	1	–	1	3
T1b	8	2	1	–	5	16
T1c	30	4	5	6	18	63
pT2	13	3	8	16	5	45 (33.8%)
pT3	–	–	–	2	1	3 (2.3%)
pT4	–	–	1	–	2	3 (2.3%)
Mean diameter (mm)	17.2	20.1	24.1	30.7	17.2	20.5
Node involvement						
N1mic		3		–		3
N1		6		14		20
N2		–		7		7
N3		–		3		3
Total involved axillae		9		24		33 (24.8%)
Mean involved nodes		1.2		4.5		
Rate of involved axilla in cN0	11.8% (9/77)					
Rate of uninvolved axilla in cN0	88.3% (68/77)					
Rate of total node involvement	32.7% (33/101)					
Distant metastases	–	–	–	–	–	–
Prognostic factors						
Estrogen receptor positive	44	8	16	22	30	120 (90.2%)
Progesterone-receptor positive	42	8	16	22	26	114 (85.7%)
Ki-67 < 20%	26	4	14	9	13	62 (46.6%)
Ki-67 ≥ 20%	26	5	2	15	19	67 (50.4%)
C-erb-B2 positive	7	2	1	4	25	39 (29.3)
C-erb-B2 negative	45	7	15	20	7	94 (70.7%)
Age						
65–69	25	3	5	7	9	49
70–74	15	4	8	8	8	43
75–79	9	–	2	4	5	20
≥80	3	2	1	5	10	21
Mean age	70.9	72.8	69.8	73.5	75.1	
Total	**52**	**9**	**16**	**24**	**32**	**133**
	61		40		32	

Table 3
Adjuvant therapy and follow-up results.

	SLND		ALND		NO surgery	Total
	pN0	pN+	pN0	pN+	pNx	
Whole breast irradiation	21	2	4	4	6	37 (27.8%)
Tamoxifen	41	6	15	17	21	100 (75.2%)
Ipsilateral breast tumor recurrence	1	–	–	1	1	3 (2.3%)
Axillary recurrence	–	–	–	–	–	0 (0%)
Deaths for other causes	–	–	1	–	1	2 (1.5%)
Total	52	9	16	24	32	133
	61		40			

Table 4
Features of patient with metastatic sentinel node.

Patients	Age	Site	Surgery	Excised Lns	Diagnosis	Max diameter	*T*	*N*	Grading	ER	PgR	Ki67%	C-erb-b2
S.S.	68	Right upper-outer quadrant	BCS	1	IDC	16	1c	1	2	90	80	15	Neg
C.R.	74	Right multicentric	TM	2	3 IDC + DCIS	50	m2	1mic	3	90	80	25	Neg
T.M.L.	65	Left upper-outer quadrant	BCS	5	IDC	26	2	1mic	3	Neg	<3	40	Neg
V.M.P.	72	Left multifocal	TM	2	2 IDC	30	m2	1mic	3	85	60	40	Pos
B.I.	73	Right upper-outer quadrant	BCS	5	IDC	16	1	1	2	90	80	<10	Pos
C.P.	66	Right upper-outer quadrant	TM	5	IDC	8	1	1	3	70	50	15	Neg
M.A.	70	Left lower-outer quadrant	BCS	1	IDC	10	1	1	1	90	90	<10	Neg
G.I.	88	Left lower-outer quadrant	BCS	1	IDC	13	1	1	2	90	50	40	Neg
D.M.	80	Right multifocal	BCS	5	IDC + DCIS	12	1	1	3	90	90	20	Neg
Mean value	72.8			3		20.1							

suitability of older patients for surgery [18,19]. Measures of global functional ability are effective in predicting life expectancy, but they are time consuming and require specialist interpretation, outside the experience of most breast surgeons, thus we let geriatrics to evaluate our patients [20]. In our experience we did not consider the age per se the only factor in the decision-making process, but we valorized the overall status and the communication with the patient. Personal choice has to be favored to assess a proper awareness of the disease process and all available treatment options [21,22].

BCS was feasible in most patients (75.9%) and determined a low rate of recurrence (2.3%). The most frequent tumors were pT1c (47.4%), ER positive (90.2%), PR positive (85.7%), HER2 negative (70.7%); whilst ki-67 > 20% showed a slight prevalence.

27.8% of patients underwent whole breast irradiation according to age and functional status. Tamoxifen was administered in 75.2% of patients with good results in local control. The CALGB 9343 trial demonstrated no benefit of radiotherapy for 70 year old with T1N0 ER-positive tumors after BCS and tamoxifen, representing a good model for population in study [23,24]. We performed ALND or SLNB in 77 clinically negative axillae, resulting in 68 avoidable interventions. If axillary surgery was avoided for these patients' we would have lost 11.8% of metastatic axillary nodes (7.8% without considering micro-metastases). Maybe the same loss occurred in no surgery group, where axillary dissection was omitted. The prognosis of all groups: pN0, pN+ or pNx seems to be superimposable, regardless from treatment. This suggests that axillary surgery could be safely omitted without affecting patient' s survival, even if it remains highly utilized by surgeons [25–27]. In addition to this studies indicate a local progression of less than 10% (2.3% in our experience), which, in most cases can be controlled with either further surgery or radiotherapy without affecting overall survival [28]. NSABP B-04 trial found that, although 40% of the patients who underwent ALND had pathologically involved nodes, only 18% of patients who did not undergo dissection experienced a clinically axillary failure [23,29–34]. In our experience in elderly the rate of involved nodes was only 11.8% and the rate of axillary recurrence was 0%, maybe due to an older and smaller cohort, a shorter follow-up. The low number of axillary failure was maybe due to the endocrine therapy and the whole breast irradiation. The patients with loco-regional recurrence were treated with salvage mastectomy and are still alive. Patients with positive sentinel node were not treated with a further axillary dissection and they haven't experienced any axillary recurrence to date. Minimally invasive treatment options for the breast cancer in elderly seems not worsening prognosis, in terms of DFS and OS.

5. Conclusions

The omission of axillary dissection in elderly breast cancer leads to a lack of staging as well as prognostic information. However, it does not impact treatment decision. Disease free survival and overall survival are the same both in patients with treated and no treated axilla. Even if evidences about the treatment of breast cancer in elderly are still controversial, each patient deserves a multidisciplinary approach to discuss the best treatment option. Current guidelines should be followed in over 65 with good functional status and long life expectancy patients, but as recent studies suggest a more sparing surgery should be proposed to all over 65 patients suffering from poorer performance status.

Ethical approval

Ethical approval was requested and obtained from the University of Naples Federico II ethical committee.

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Author contribution

Limite Gennaro: Participated substantially in conception, design, and execution of the study and in the analysis of data, reviewing the manuscript.

Di Micco Rosa: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Sollazzo Viviana: Participated substantially in the analysis and interpretation of data.

Esposito Emanuela: Participated substantially in the analysis and interpretation of data, reviewing the manuscript.

Cervotti Maria: Participated substantially in the analysis and interpretation of data.

Compagna Rita: Participated substantially in the analysis and interpretation of data, in reviewing and drafting and editing the manuscript.

De Werra Carlo: Participated substantially in the analysis and interpretation of data.

Amato Bruno: Participated substantially in analysis and interpretation of data, in reviewing and drafting and editing the manuscript.

Forestieri Pietro: Participated substantially in reviewing the manuscript.

Conflicts of interest

All Authors have no conflict of interests.

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